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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,488	05/11/2001	Chamsy Sarkis	ST98023A	8713

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EXAMINER	
VOGEL, NANCY T	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/23/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,488	SARKIS ET AL.	
	Examiner	Art Unit	
	Nancy Vogel	1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,16-18 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,16-18 and 23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/11/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-7, 9, 10, 16-18, 23-33 are pending.

Receipt of preliminary amendments on 6/21/01, 10/1/01 and 10/15/01 is acknowledged.

Claim Objections

Claims 4, 23 and 33 objected to because of the following informalities: Claim 4 contains the word "neutrophic". Presumably, "neurotrophic" is intended. Claims 23 and 33 contain numerous abbreviations such as CNFT, LIF, FGF, etc. The intended compounds must be spelled out. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 25-27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. They encompass pharmaceutical compositions comprising baculovirus containing any gene which may have therapeutic use in the treatment of any neurological disorder, and methods of treating any disease of the nervous system comprising administering said baculovirus. There are a large numbers of diseases encompassed by the term "disease of the nervous system", ranging from cerebral palsy, to Alzheimer's disease, to Parkinson's disease, etc. There are a large number of genes whose products may be therapeutic for said diseases.

The nature of the invention is very complex because it is compositions and methods that are to be used to treat illness, and the treatment method includes the administration of a foreign gene in vivo, i.e. gene therapy. The list of possible diseases to treat is very large and concerns treating very complex diseases, some of which have no known treatments.

The state of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997)389:239-242) and Palu et al. (J. Biotechnol. (1999) 68:1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239 1st paragraph ; Palu et al. p.1. Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. While these references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene deliver, targeting and expression must be made before gene therapy becomes a useful technique. See Verma et al p.242, col. 2-3, ; Palu et al. pp 10-11.

The relative skill of those in the art of recombinant DNA techniques and medical treatments is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2):1-3. Furthermore, it cannot be predicted whether the claimed method comprising administration of the recombinant baculovirus would result in appropriate expression levels, in appropriate cells, such that amelioration of neurological symptoms would result. The skilled artisan at the time the present invention was made recognized the

difficulty of achieving sufficient heterologous gene expression to induce therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression. While the specification lists a large number of proteins and promoters that can be produced using the recombinant baculovirus, and shows in vitro and in vivo infection of cells with a recombinant baculovirus expressing a marker protein, there is no example of the treatment of a neurological disease, or guidance for such aspects as dosage, and method of administration, that would be required for effective treatment of any diseases of the nervous system.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a disease of the nervous system, one of skill I the art would have to determine the effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for the treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and host to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require ad large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the art of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require under experimentation by one of skill in the art to determine how to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 9, 10, 16, 17, 23, 24, 28, 29, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyce (WO9812311).

Boyce disclose a recombinant baculovirus having a baculovirus envelope protein, comprising a gene encoding a heterologous protein operatively associated with a promoter, wherein the heterologous protein may be of therapeutic interest for the treatment of neurological disease (page 3 lines 8-18). The reference discloses that said gene may encode any protein of interest, including enzymes of the urea cycle (page 2, lines 4-20), nerve growth factors, HGPRT, tyrosine hydroxylase, dopadecarboxylase, brain-derived neurotrophic fact and basic fibroblast growth factor (page 3, lines 8-18). The reference discloses that any cell-type specific promoter may be used, such as

neuron-specific enolase promoter, or tyrosine hydroxylase promoter (page 8 line 46-page 9 line 10, page 11, line 4-32). The reference discloses that a signal sequence may be used for targeting of the gene product (page 8 line 46). The reference discloses cells, or implants, including neurons, infected with said baculovirus (see page 9 line 11-26, page 18, lines12-21, page 21 last line – page 22 last paragraph, page 28, lines 35-44) .

Claims 1-4, 23, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (Biochem. J. 324:461-466 (19997)).

Li et al. disclose recombinant baculovirus comprising the gene encoding neurotropin-6 (NT-6))(see abstract and page 461, first column, second paragraph).

Claims 1-4, 23, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by DiFalco et al. (Biochemi. J. 326, 407-413 (1997).

DiFalco et al. disclose recombinant baculovirus comprising the gene encoding IGF-2. (see abstract and page 407, columns 1 and 2).

Claims 1-4, 23, 31-33 are rejected under 35 U.S.C. 102(b), as being anticipated by Meyer et al. (J. Neurochem. 62, 3, 825-833 (1994).

Meyer et al. disclose recombinant baculovirus comprising the genes encoding brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (see abstract and page 825, columns 1 and 2).

Claims 1-4, 23, 31-33 are rejected under 35 U.S.C. 102(b), as being anticipated by Fandl et al. (J. Biol. Chem. 269, 1, 755-759 (1994)).

Fandl et al. disclose recombinant baculovirus comprising the gene encoding neurotrophin-4 (NT-4) (see page 755).

Claims 1-4, 23, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (J. Biol. Chem. 267, 17, 12275-12283 (1992)).

Luo et al. disclose recombinant baculovirus comprising the gene encoding beta-nerve growth factor (see page 12275).

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Gritson et al. (Nucl. Acids Res. Vol. 25, No. 9, 1864-1865 (1997)).

Gritson et al. disclose a recombinant baculovirus comprising the heterologous nucleic acid encoding beta-glucuronidase (see abstract and page 1880, 1st column, last paragraph – 2nd column, line 12).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyce et al. (WO 98/11243) in view of Gritson et al. (Nucl. Acids Res. Vol. 25, No. 9, 1864-185, (1997)).

Boyce et al. disclose recombinant baculovirus comprising a envelope protein which is foreign to a baculovirus, i.e. VSV (see page 3, lines 25- page 4 line 4). Boyce et al. disclose said recombinant baculovirus, further comprising a reporter gene, such as lacZ (see pages 71-74). Boyce et al. does not teach the recombinant baculovirus containing beta-glucuronidase.

However, Gritson et al. teach recombinant baculovirus containing the gene encoding beta glucuronidase as a reporter, or marker (see abstract).

It would have been obvious to one of skill in the art to substitute the gene encoding beta-glucuronidase for the lacZ gene in the recombinant baculovirus disclosed by Boyce, in order to obtain a baculovirus having the known and useful property of easily assayable expression of the beta-glucuronidase. The substitution of one well known marker gene for another would have been obvious to one of ordinary skill in the art, and was routine at the time of the invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (703) 308-4548. The examiner can normally be reached on 7:30 - 4:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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TERRY MCKELVEY
PRIMARY EXAMINER